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Impact of obesity on arteriovenous fistula outcomes in dialysis patients

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Fistula use for dialysis is less frequent among obese than non-obese patients. This discrepancy may be due to a lower rate of fistula placement in obese patients, a higher primary failure rate (fistulas that are never usable for dialysis), or a higher secondary failure rate (fistulas that fail after being used successfully for dialysis). Using a prospective, computerized vascular access database, we identified all patients receiving a first fistula or graft at our institution during a 2-year period. The access outcomes were compared between obese (body mass index (BMI) $\geqslant$30 kg/m^2) and non-obese (BMI$<$30 kg/m^2) patients. Fistula placement was equally likely between obese and non-obese patients (47.4 vs 47.1%). The primary failure rate of fistulas was similar in both groups (46 vs 41%, $P=0.45$). Among those fistulas that were usable for dialysis, the secondary survival was worse in obese patients (hazard ratio 2.74; 95% confidence interval (CI), 1.48–7.90; $P=0.004$). Secondary fistula survival in obese vs non-obese patients was 68 vs 92% at 1 year, 59 vs 78% at 2 years, and 47 vs 70% at 3 years. On multiple variable survival analysis with age, sex, race, diabetes, coronary artery disease, peripheral vascular disease, fistula location, surgeon, and obesity in the model, obesity was the only significant factor predicting secondary fistula failure (hazards ratio 2.93; 95% CI, 1.44–5.93; $P=0.004$). In conclusion, long-term fistula survival is worse in obese than non-obese patients, owing to a higher secondary failure rate.

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Several clinical studies have reported a lower prevalence of fistulas among obese hemodialysis patients, as compared to their non-obese cohorts.[1–3] Increasing the prevalence of fistulas requires increasing fistula placement, adequate maturation of new fistulas, and successful long-term cannulation of the fistulas by the dialysis staff.[4] Thus, there are several potential explanations for the lower fistula prevalence among obese patients. First, it is possible that fistulas are less likely to be placed in obese patients. Second, fistulas placed in obese patients may be more likely to have a primary failure (never be usable for dialysis). Third, fistulas in obese patients may be more likely to have a secondary failure after initially being used successfully for dialysis. The published studies, owing to their cross-sectional research design, cannot adequately distinguish among these three potential scenarios. Such an analysis would require longitudinal follow-up of fistulas placed in obese and non-obese patients with chronic kidney disease.

The goal of the present study was to compare the outcomes of arteriovenous fistulas placed in obese and non-obese patients, and to elucidate the reasons for the lower fistula use among obese patients.

RESULTS

During the 2-year study period, a first fistula was placed in 183 patients and a first graft in 205 patients. Thus, among the first vascular accesses placed, 47.2% were fistulas. As compared to patients with graft placement, those receiving a fistula were more likely to be male and white (Table 1). However, patient age, frequency of diabetes, coronary artery disease, peripheral vascular disease, and obesity did not differ significantly between patients receiving a fistula and those receiving a graft. Fistula placement was equally likely in the obese and non-obese patient groups (47.4 vs 47.1%, respectively, of vascular accesses placed). On multiple logistic regression analysis, only two clinical factors predicted a lower likelihood of fistula placement: black race (odds ratio (OR) 0.50; 95% confidence interval (CI), 0.30–0.86) and female sex (OR 0.60; 95% CI, 0.40–0.90).

The fistula study population included 54 obese and 129 non-obese patients. The clinical characteristics of both groups are compared in Table 2. The obese patients were

Table 1 | Clinical features of patients receiving a fistula vs a graft

	Fistula	Graft	*P*-value
N patients	183	205	—
Age	55±14	55±15	0.71
Sex			0.007
Male	109 (60%)	94 (46%)	—
Female	74 (40%)	111 (54%)	—
Race			0.01
Black	139 (76%)	178 (87%)	—
White	42 (24%)	27 (13%)	—
Diabetes			0.56
Yes	107 (58%)	112 (55%)	—
No	79 (42%)	93 (45%)	—
CAD			0.12
Yes	55 (30%)	77 (38%)	—
No	128 (70%)	128 (62%)	—
PVD			0.86
Yes	23 (12%)	27 (13%)	—
No	160 (88%)	178 (87%)	—
Obese			0.96
Yes	54 (30%)	60 (29%)	—
No	129 (70%)	145 (71%)	—

CAD, coronary artery disease; PVD, peripheral vascular disease.

similar to the non-obese patients in terms of their age, sex, race, frequency of coronary artery disease and peripheral vascular disease. The likelihood of fistula placement before dialysis was similar in both groups, as was the fistula location and frequency of vein transposition. However, diabetes was more common among the obese patients. On multiple logistic regression analysis, the only variable that was associated with obesity was the presence of diabetes (OR 3.30; 95% CI, 1.61–6.74).

The diameters of the arteries and veins used to create the fistulas were similar between the obese and non-obese patient groups, whether one examined forearm or upper arm fistulas (Table 3). Primary fistula failure (inability to ever use the fistula for dialysis, owing to technical failure, early thrombosis, or failure to mature) occurred at a similar rate in the two groups (Table 4). However, among those patients whose fistulas were successfully used for dialysis for at least 1 month, the secondary fistula survival was substantially lower in obese patients, as compared with their non-obese controls (Figure 1). The hazard ratio for secondary fistula failure in obese patients was 2.74 (95% CI, 1.48–7.90; $P=0.004$). Secondary fistula survival did not differ between overweight (body mass index (BMI) 25.0–29.9 kg/m^2) and normal weight (BMI 18.5–24.9 kg/m^2) patients (hazard ratio, 1.13; 95% CI, 0.42–3.06; $P=0.80$) (Figure 1). On multiple variable survival analysis with age, sex, race, diabetes, coronary artery disease, peripheral vascular disease, fistula location, surgeon, and obesity in the model, obesity was the only significant factor associated with secondary fistula failure (hazards ratio 2.93; 95% CI, 1.44–5.93; $P=0.004$). To evaluate the possibility that the hazard of fistula failure differs over time, a time-by-obesity interaction variable was defined, and the Cox model re-estimated after adding this variable. The interaction variable yielded a *P*-value of 0.065.

Table 2 | Clinical features of fistula study patients

	Obese	Non-obese	*P*-value
N patients	54	129	—
Age	56±12	56±16	0.92
Sex			0.09
Male	27 (50%)	82 (64%)	—
Female	27 (50%)	47 (36%)	—
Race			0.17
Black	45 (83%)	94 (73%)	—
White	9 (17%)	33 (27%)	—
Diabetes			0.0007
Yes	41 (76%)	63 (49%)	—
No	13 (24%)	66 (51%)	—
CAD			0.25
Yes	13 (24%)	42 (33%)	—
No	41 (76%)	87 (67%)	—
PVD			0.55
Yes	8 (15%)	15 (12%)	—
No	46 (85%)	114 (88%)	—
Pre-HD?			0.33
Yes	26 (48%)	52 (40%)	—
No	28 (52%)	77 (60%)	—
Fistula location			0.90
Forearm	29 (54%)	68 (53%)	—
Upper arm	25 (46%)	61 (47%)	—
Vein transposition[a]			0.45
Yes	8 (15%)	14 (11%)	—
No	46 (85%)	115 (89%)	—

CAD, coronary artery disease; Pre-HD, fistula placed before initiation of dialysis; PVD, peripheral vascular disease.

[a]Transposition of the vein, either as a primary fistula procedure or as a second procedure for fistulas that were too deep for safe cannulation.

Table 3 | Preoperative vascular diameters in obese and non-obese patients, sorted by fistula location

	Obese patients	Non-obese patients	*P*-value
Forearm fistula			
Artery diameter	0.26±0.04	0.26±0.04	0.98
Vein diameter	0.31±0.05	0.31±0.04	0.83
Upper arm fistula			
Artery diameter	0.48±0.08	0.49±0.09	0.88
Vein diameter	0.44±0.11	0.41±0.09	0.24

DISCUSSION

The present study examined the reasons for a lower arteriovenous fistula prevalence among obese hemodialysis patients. Fistula placement could not account for this

Table 4 | Initial fistula outcomes

	Obese	Non-obese
Total number	54	129
Successful use for dialysis (⩾1 month)	29 (54%)	76 (59%)
Primary failure	25 (46%)	53 (41%)
Technical failure	5	7
Early thrombosis	14	20
Failure to mature	6	25
Steal	0	1

No difference in outcomes between groups, P=0.45.

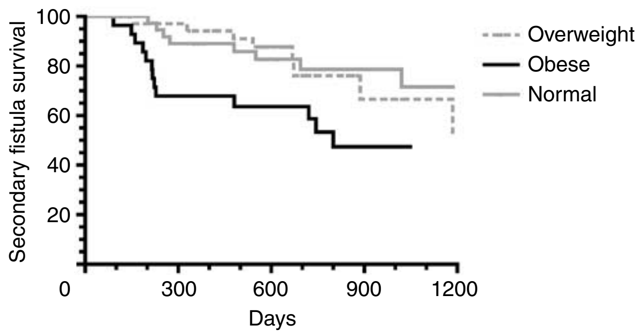

Figure 1 | Secondary survival of fistulas in obese and non-obese patients. Secondary survival was calculated from fistula placement to permanent fistula failure, after excluding fistulas with primary failure (never usable for dialysis). Obese, BMI $>30\,kg/m^2$; overweight, BMI 25.0–29.9 kg/m^2; normal weight, BMI 18.5–24.9 kg/m^2. We omitted seven patients who were underweight (BMI < 18.5). $P=0.004$ for obese vs non-obese patients, and $P=0.80$ for overweight vs normal weight patients, by log rank test.

difference, as the proportion of obese and non-obese patients having a fistula placement was virtually identical. Although obesity may make it more challenging for the surgeon to identify suitable vessels for fistula construction, this problem can be overcome by the routine use of preoperative vascular mapping. We have previously documented that the frequency of fistula placement was similar in obese and non-obese patients when vascular mapping was employed.[5] A second potential explanation for the lower prevalence of fistulas among obese patients is that new fistulas are less likely to mature adequately for successful cannulation for dialysis. This explanation also seems unlikely, given that the primary failure rate of new fistulas was very similar between obese and non-obese patients (Table 4). This observation is in keeping with a previous report from our institution finding that successful initial use of fistulas for dialysis was equally likely in obese and non-obese dialysis patients.[5]

Finally, it is possible that the secondary failure rate of fistulas (after initial successful use for dialysis) is higher among obese patients. This hypothesis was confirmed by comparing the cumulative survival rates of fistulas in the two study groups (Figure 1). The inferior survival of fistulas in obese patients was evident within the first few months, and sustained for at least 3 years. Why might fistulas failure be more likely in obese patients? One potential explanation is that fistulas created in obese patients utilized smaller vessels, as compared with fistulas placed in non-obese patients. This seems unlikely, given the similarity between the arterial and venous diameters in the two patient groups (Table 3). A second possibility is that obese patients may require vein transposition for fistula creation more frequently, and transposed vein fistulas have secondary survival inferior to that obtained in fistulas using veins in their native location.[6] However, in the present study, there was no difference in the proportion of obese and non-obese patients requiring vein transposition for fistula creation (Table 2). A third potential explanation is that secondary fistula failure is more likely in obese patients as a consequence of needle infiltration during cannulation. However, a recent report from our institution found no difference in the frequency of fistula infiltration between obese and non-obese patients.[7] A fourth possibility is that a hypercoagulable state in obese patients increases the likelihood of fistula thrombosis. This hypothesis would be consistent with the increased tendency for early fistula thrombosis (56 vs 38%, $P=0.13$) in obese patients with primary fistula failure (Table 4). All secondary fistula failures were due to thrombosis. Very few of the clotted fistulas underwent attempted thrombectomy. Thus, it was not possible to determine whether the excess fistula failure in the obese patients was due to a hypercoagulable state or to accelerated neointimal hyperplasia.

A final possibility is that myointimal hyperplasia is more aggressive in obese than non-obese patients, and that this results in earlier onset of stenosis, leading to fistula thrombosis. This hypothesis would be consistent with the association between obesity and increased plasma levels of the inflammatory marker, C-reactive protein, which has been observed in both the normal population,[8,9] as well as in patients with chronic kidney disease or dialysis.[10,11] Moreover, a preliminary report suggested a pathogenetic role for C-reactive protein in the induction of myointimal hyperplasia.[12] The retrospective nature of the present study precluded an evaluation of the association between C-reactive protein levels and secondary fistula failure. The expanded Cox model did not show a significant interaction between time and the effect of obesity on secondary fistula failure ($P=0.065$). However, the suggestion that the hazard for fistula failure is greatest in the first 6 postoperative months merits future investigation.

There was no difference in secondary fistula survival between overweight and normal weight patients (Figure 1). This observation suggests that mild increases in BMI do not represent a risk factor for fistula failure. Thus, only substantial increases in BMI ($\geqslant 30\,kg/m^2$) appear to increase the likelihood of secondary fistula failure.

Because this study represents the fistula outcomes from a single dialysis center, the findings may not generalize to all dialysis centers. For example, in centers not using routine preoperative vascular mapping, the frequency of fistula placement may be lower in obese, as compared to non-obese, patients. Moreover, preoperative vascular mapping may affect the risk of fistula failure in obese patients. A previous analysis from our center, at a time when preoperative vascular mapping was not being performed, observed a trend for higher primary fistula failure (non-maturation) in obese, as compared with non-obese patients (65 vs 45%, $P=0.07$).[13] In contrast, following the implementation of routine preoperative mapping, we no longer observed such an effect (primary fistula failure in obese vs non-obese patients, 48 vs 43%, $P=0.61$).[5] Similarly, three subsequent studies from centers using preoperative vascular mapping found no association between BMI and risk of primary fistula failure.[14–16] In contrast to the present study, the one by Dixon *et al.*[14] found no association between BMI and secondary fistula failure. The patients in that study were predominantly ($>90\%$) white, whereas the ones enrolled in the current study were predominantly black. Thus, obesity may be a risk factor for secondary fistula failure in black, but not white patients. Owing to the small number of white patients in the present study, it is difficult to assess this potential explanation for the discrepant findings. Finally, another observational study found no association between BMI and secondary fistula failure;[17] it was not stated, however, whether preoperative vascular mapping had been used.

Regardless of the precise mechanism involved, the association between obesity and inferior fistula outcomes has important clinical implications. This discrepancy may in part explain some geographic discrepancies in fistula prevalence. For example, the Dialysis Outcomes and Practice Pattern Study reported that obesity was more common in the USA than in Europe,[2] and this may, in part, contribute to the lower prevalence of fistulas in the USA. From a practical point of view, obese patients receiving an arteriovenous fistula may require heightened vigilance for evidence of fistula stenosis, and may derive the greatest benefit from potential pharmacologic prophylaxis.

MATERIALS AND METHODS

Patient population

About 450 patients receive chronic hemodialysis under the care of University of Alabama at Birmingham nephrologists. These patients receive dialysis at one of five dialysis units in the metropolitan Birmingham area. Initial vascular access placements and subsequent access revisions are performed by University of Alabama at Birmingham transplant surgeons and interventional radiologists or nephrologists.

Vascular access management

Four surgeons performed all the vascular access operations. Each patient referred for a new vascular access first underwent preoperative sonographic vascular mapping. The results of the vascular mapping studies were provided to the surgeons, to assist them in planning the optimal access type and location.[4,5,18] Creation of a fistula required a minimum artery diameter of 2.0 mm, a minimum vein diameter of 2.5 mm, and absence of stenosis or thrombosis of the vein proximal to the intended anastomotic site. The type of fistula placed, in order of preference, was a radiocephalic fistula, brachiocephalic fistula, or transposed brachiobasilic fistula. In some patients, a vein transposition (superficialization) was performed as a second surgical procedure if the fistula was too deep for safe cannulation. Grafts were placed only when there were no suitable vessels for creation of a fistula. All patients were referred for creation of a vascular access, regardless of their degree of obesity. All access procedures were scheduled by two full-time vascular access coordinators, who recorded the procedures in a prospective computerized database.[19]

The surgeons usually evaluated each patient's new fistula 1–2 weeks following its creation. In addition, new fistulas were assessed clinically for their maturation and suitability by the nephrologists and dialysis nurses. If there was uncertainty about the suitability of a fistula for cannulation, a postoperative ultrasound was obtained to measure the diameter of the fistula, the access blood flow, and the depth from the skin. In general, a fistula was considered to be adequately developed if the ultrasound measurements included a diameter $\geqslant 4$ mm, blood flow $\geqslant 500$ ml/min, and perpendicular distance from the skin $\leqslant 5$ mm.[20] In addition, the ultrasound was used to screen for potentially remediable causes of immature fistulas. These included stenotic lesions, large competing veins, or fistulas that were too deep to be cannulated safely.[21] The ultrasound findings were followed in some patients by specific salvage procedures by the surgeon or radiologist. These could include angioplasty or surgical revision of a stenotic lesion, ligation of a competing vein, or superficialization of a deep fistula. Fistulas were usually cannulated for dialysis 8–12 weeks following their creation. If an immature fistula had no remediable lesions or failed to develop despite the salvage procedure, the patient was referred to the surgeon for placement of a new vascular access.

Patients in whom there was a clinical suspicion of fistula stenosis were referred for a diagnostic fistulogram. The clinical criteria included abnormalities in physical examination, difficulties in the dialysis treatment, or an unexplained decrease in K_t/V.[22] A $\geqslant 50\%$ stenotic lesion was considered hemodynamically significant and treated by angioplasty. Elective surgical revision was performed if the angioplasty was technically unsatisfactory. A fistula that could not be salvaged either radiologically or surgically was abandoned, and the patient was referred for placement of a new vascular access.

Data collection and analysis

The prospective access database was used to identify a comprehensive list of all vascular accesses placed during a 2-year time period (1 January 2002 to 31 December 2003). It was also used to track subsequent surgical or radiologic interventions for each access placed. Each patient's medical record was reviewed for research purposes after obtaining Institutional Review Board approval.

Fistulas were considered *adequate for dialysis* if they were cannulated successfully for dialysis with two needles for at least 1 month, and within 6 months of their creation.[13] *A technical failure* was defined as the inability of the surgeon to construct a vascular access or thrombosis within 24 h of its creation. Early thrombosis was defined if a fistula clotted within 12 weeks of its creation, and before being used for dialysis. Fistulas were deemed to have *failed to mature*, if they were not usable for dialysis within 6 months of placement, in the absence of technical failure or early thrombosis. Fistulas were deemed *inadequate for dialysis* (or primary failures) if there was a technical failure, early thrombosis, or failure to mature. The fistula outcome was considered *indeterminate* if the patient had not started dialysis at the time of data analysis or if the patient died, moved to a non-participating dialysis unit, was lost to follow-up, or switched to peritoneal dialysis before the adequacy for dialysis could be assessed. *Secondary failure* was defined as permanent failure of a fistula, after it had achieved primary adequacy for dialysis.

Demographic and clinical information was collected on each patient, including age, sex, race, and presence of diabetes, coronary artery disease, or peripheral vascular disease. BMI was calculated from standard formulae. Patients were considered obese if their BMI was $\geqslant 30\,kg/m^2$, and non-obese if their BMI was $<30\,kg/m^2$.

During the 2-year study period, 262 fistulas were placed in 226 patients. For the purpose of this study, only the first fistula placed in each patient was included in the analysis. We excluded 29 patients with indeterminate fistula outcomes, and 14 with unknown or indeterminate BMI. The remaining 183 patients constituted the fistula study population. During the same study period, 205 first grafts were placed, and these patients constituted the graft study population. Thus, among all first permanent accesses placed during the study period, 47% were fistulas and 53% were grafts.

Statistical analyses

The clinical characteristics were compared between obese and non-obese patients using Student's *t*-tests or χ^2 analysis, with a *P*-value <0.05 considered to be statistically significant. Multiple logistic regression analysis was used to evaluate which factors were associated with fistula placement and with obesity. Secondary fistula survival was calculated from the date of fistula creation to the date of permanent failure, regardless of the number of interventions required to achieve long-term patency. Survival analysis techniques were used to model fistula survival time, and the log rank test used to compare the survival of patient subgroups. Univariate Cox proportional hazard models were fit. Hazard ratios and their associated 95% CI were computed. Finally, multiple variable survival analysis was used to model the association between the clinical variables and secondary fistula survival.

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